

Adaptation of the brain to hypoglycemia: Does the brain stand by for the next hypoglycemia event?

Diabetes mellitus is associated with a variety of complications, including neuronal disorders. Studies have shown that type 1 diabetes mellitus patients are at higher risk for cognitive dysfunction, but the mechanism underlying this greater risk has not yet been fully elucidated. Most type 1 diabetes mellitus patients suffer from hypoglycemia repeatedly over the course of treatment. Severe hypoglycemia causes acute brain malfunction that leads to coma and is sometimes life-threatening. Although it has been reported that patients who have a history of hypoglycemic events are more likely to develop dementia¹, patients with type 1 diabetes mellitus showed minimal cognitive dysfunction in the Diabetes Control and Complications Trial (DCCT) study². Thus, the influence of hypoglycemia on physiological function of the brain is disputable.

van de Ven *et al.*³ reported that type 1 diabetes mellitus patients showed altered cerebral glucose metabolism during hypoglycemia compared with healthy controls. In their previous study, they used ¹³C magnetic resonance spectroscopy to explore cerebral glucose metabolism during hypoglycemic glucose clamp in healthy subjects and evaluated the tricarboxylic acid cycle flux (V_{TCA}). Their results showed that there was no change in V_{TCA} in euglycemic or hypoglycemic conditions, and they concluded that acute moderate hypoglycemia does not affect glucose metabolism in the brains of healthy subjects.

In the present study, van de Ven *et al.*³ carried out a similar examination in

participants with type 1 diabetes mellitus. They evaluated V_{TCA} during euglycemic and hypoglycemic glucose clamp experiments, and their results were consistent with those of the previous study: cerebral glucose metabolism was maintained during hypoglycemia in type 1 diabetes mellitus patients as well. Although the V_{TCA} level during hypoglycemia was approximately the same as that observed under normal glucose concentrations, V_{TCA} under hypoglycemic conditions was significantly higher in type 1 diabetes mellitus patients than in healthy controls.

When glucose is present at physiological concentrations, the brain derives nutrients mostly from glucose; thus, severe hypoglycemia causes functional impairment and sometimes irreversible damage to the brain. Although most type 1 diabetes mellitus patients experience hypoglycemia, the frequency of hypoglycemia is not related to a higher risk of cognitive impairment. On the basis of this result, van de Ven *et al.*³ hypothesized that the brain physiologically adapts to protect itself from hypoglycemia. To test this hypothesis, they carried out euglycemic and hypoglycemic glucose clamp on type 1 diabetes mellitus patients and compared their cerebral glucose metabolism with that of healthy subjects. Their findings showed that type 1 diabetes mellitus patients have a higher V_{TCA} and greater lactate intake during hypoglycemia.

These results suggest that the brain can increase its usage of alternative energy sources when glucose is not sufficient, and this adaptive response can be promoted by repetitive hypoglycemia. In clinical practice, this effect might be the basis of a new method for decreasing consciousness disturbance or reducing cerebral damage caused by glucose insufficiency during

hypoglycemic attack in type 1 diabetes mellitus patients. The mechanism of this increased cerebral glucose metabolism in type 1 diabetes mellitus was not well investigated in this study, and it is not clear whether the effect was caused by hypoglycemia itself or other features of type 1 diabetes mellitus, such as shortage or excess of hormones, or changes in the autonomic nervous system. It will be important to investigate the mechanism of increased cerebral glucose metabolism to determine whether it can be put to practical use to prevent or alleviate the hypoglycemic unconsciousness that impairs the quality of life of type 1 diabetes mellitus patients.

van de Ven *et al.*³ also showed increased lactate usage during hypoglycemia. Neuronal cells are thought to utilize lactate as a nutrient⁴. When cerebral function is highly activated, glucose is consumed mainly by astrocytes, and neuronal cells take up lactate that is provided by astrocytes through the glycolysis pathway⁵. Thus, because neuronal cells are capable of utilizing lactate as a nutrient, it might also be valuable to investigate whether the lactate uptake rate is increased in type 1 diabetes mellitus patients compared with normal controls, and whether recurrent hypoglycemia could increase the uptake temporarily or permanently. Such an investigation would enhance our understanding of this cerebral metabolic change.

Most of the participants examined in this study showed higher V_{TCA} than those in the previous study. This might show that type 1 diabetes mellitus patients have a higher rate of glucose metabolism regardless of glucose level, although significant changes were observed only during hypoglycemia. Additionally, although the clamp tests were carried out using the same protocol,

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it is possible that other factors, such as seasonal changes or technical problems, could have affected the results.

In this study, van de Ven *et al.*³ suggested that the brain undergoes adaptive change during hypoglycemia in type 1 diabetes mellitus patients. The authors carried out hypoglycemic clamp experiments with a glucose concentration (3.0 mmol/L) low enough to trigger mild or moderate hypoglycemia. Although there is some compartmental variation, the glucose concentration of extracellular fluid in brain tissue is thought to be approximately 2 mmol/L or lower⁶. Thus, the temporary mild hypoglycemic condition in this study might not have caused an adequate shortage of glucose in the brain tissue.

From a practical viewpoint, there seems to be a group of type 1 diabetes mellitus patients who can be characterized as extremely difficult to control, showing fluctuations in their plasma glucose level, hypoglycemia unawareness and frequent, sudden unconsciousness. These symptoms would be caused mainly by completely or highly impaired insulin

secretion. Although there are many other factors that can affect glucose instability, it might be useful to investigate the relationship between this adaptive effect (V_{TCA} increase) and the clinical features of type 1 diabetes mellitus, such as insulin secretion or glucose instability.

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